REMARKS

Applicants appreciate the recognition that there is no suggestion in the art for compositions or methods where the β subunits are derived from the same hormone. Claims 10 and 21 were indicated allowable over the art on this basis. This was confirmed at the interview. Accordingly, independent claims 1, 11 and 12 have been amended to read on this allowable subject matter. This required no amendment to claims 2-5 (although claims 4 and 5 have been amended for other reasons); claim 6 has been amended to conform to this limitation; claim 7 simply for clarity; claim 8 has been amended to conform as has claim 10. No amendment was required to claims 21-24 for this reason (although a typographical error has been corrected in these claims) and claims 25-28, which are inconsistent with this limitation have been canceled.

New claims 29 and 30 are directed to the alternative possibilities as compared to claim 4 and new claims 31-42 are specific embodiments of the alternatives in claims 4, 29 and 30. New claims 42 and 43 are presented in accordance with the discussion at the interview which resolved an issue regarding the DeRosa document. It was agreed that this document would not be citable as representative of a method to enhance fertility in an individual being treated for enhanced fertility. Accordingly, new claims 43-44 have been added.

The claims withdrawn from consideration have not been canceled as they represent species of the generic claims. In the event that the generic claims are found allowable, it is believed the species claimed may be rejoined.

The claims have been amended to delete the objected-to phrase "lowered LH agonist activity" and to correct a typographical error. No new matter has been added and entry of the amendment is respectfully requested.

Formal Matters - Species Election

In reviewing the record, applicants question the withdrawal from consideration of claims 4, 7-9, 22-24 and 26-28. In a species election, acknowledged in the Office action mailed 8 May 2002, applicants had elected the species wherein both β^1 and β^2 are FSH agonists. It appears that the generic claims have been examined on the basis of art which describes combination therapies which involve the use of FSH and hCG (Seethalakshmi) and putatively LH and FSH (DeRosa) although the actual composition used by DeRosa has not been established on the record. Since the claims have been examined on the basis of a species other than that elected, it is believed that the claims withdrawn from consideration should be rejoined for the purposes of the examination. The explanation provided by the Examiner at the interview is appreciated; applicants understand that rejoinder depends on there being an allowable generic claim. In view of the acknowledgement that claims where both β subunits are derived from the same hormone are not suggested by the art, and the corresponding amendments to the claims, it will be apparent that claims 22-24 are also in a position for allowance, and that the additional remaining claims should be rejoined.

The Rejections Under 35 U.S.C. § 112, Paragraph 2

Claims 1, 11 and 12 were considered indefinite because the negative limitation was considered unclear. It is believed that this rejection is now moot in view of the amendment to the claims. Proposed new claim 43 has also been modified from the original form presented in claims 1, 11 and 12 to exclude the possibility of one of β^1 and β^2 being a CG agonist and the other being an FSH agonist.

Claims 6, 8 and 10 were considered indefinite by virtue of a phrase which is now deleted from the claims and the typographical error in claim 21 (and claims 22-24) has been corrected. Thus, the rejection under this section of the statute may properly be withdrawn.

The Rejections Over the Art.

In view of the acknowledgement, kindly made by the Office, that claims limited to instances where both β^1 and β^2 are derived from the same glycoprotein hormone are not suggested by the art, the rejections over the art are moot as applied to claims 1-12, 21-24 and 29-42. It is believed that the rejections may be withdrawn with respect to new claims 43-44.

With respect to the rejection where the primary reference is the paper by Seethalakshmi, reconsideration of the relevance of this paper is requested, as the combination suggested in this paper is excluded specifically from claim 43. This document requires the combination of hCG and FSH dimers, which are, as dimers, agonists of FSH and hCG activity. This possibility is not present in claim 43, and thus the disclosure of the primary document is excluded, as is the disclosure of the secondary documents, which require presence of β subunits that are the native forms (and thus agonists).

With respect to the rejection wherein the primary reference is DeRosa, applicants appreciate the suggestion made by the Examiner at the interview that the claim be reworded to clarify that the method is applicable to those undergoing treatment for enhanced fertility, a class which excludes that treated by DeRosa.

In addition, if the Office is correct that the combination used by DeRosa is in fact LH and FSH, even if DeRosa is combined with Hyde or Ben-Menahem, no suggestion for the invention results; DeRosa, according to the Office, describes the combination of FSH and LH, the single-chain forms of Hyde involve FSH and hCG agonist forms which are excluded from the claims.

CONCLUSION

The suggestions for modification of the claims made by the Examiner at the interview have been adopted and the claims have been amended accordingly.

It is therefore believed that all pending claims, claims 1-12, 21-24 and 29-44 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 295002005900.

Respectfully submitted,

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By: Kate H. Murashige

Kate H. Murashige
Registration No. 29,959

Morrison & Foerster LLP
3811 Valley Centre Drive, Suite 500
San Diego, California 92130-2332
Telephone: (858) 720-5112
Facsimile: (858) 720-5125

EXHIBIT A. - VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

1. (Twice amended) A method to provide a subject with [different] glycoprotein hormone activities which method comprises administering to a subject in need of said activities a composition of the formula:

$\beta^2 \approx \alpha\text{-(linker)}_m\text{-}\beta^1$ (1); or

$\beta^1\text{-(linker)}_m\text{-}\alpha \approx \beta^2$ (2)

wherein each of β^1 and β^2 has the amino acid sequence of the β subunit of a vertebrate glycoprotein hormone, or a variant thereof;

"α" has the amino acid sequence of the α subunit of a vertebrate glycoprotein hormone or a variant thereof;

"linker" is a linker moiety; and

"≈" is a noncovalent link between α and β^2;

m is 0 or 1;

wherein each of β^1 and β^2 [confer a different activity on said composition,

with the proviso that if β^1 is CGβ then β^2 is not FSHβ] is the native β subunit of the same glycoprotein hormone or a variant thereof.

4. (Amended) The method of claim 1 wherein one of β^1 and β^2 confers agonist activity and the other confers antagonist [activities] activity.

5. (Amended) The method of claim 1 wherein said subject is [in need of] being treated for enhanced fertility.

6. (Twice amended) The method of claim 5 wherein

both β^1 and β^2 confer FSH agonist activity on said composition; or

both β^1 and β^2 confer CG agonist activity; or

both β^1 and β^2 confer LH antagonist activity[; or

one of β^1 and β^2 confers FSH agonist activity and the other confers LH antagonist activity or lowered LH agonist activity; or

one of β^1 and β^2 confers FSH agonist activity and the other confers CG agonist activity; or

one of β^1 and β^2 confers LH antagonist activity or lowered LH agonist activity and the other confers CG agonist activity].

7. (Amended) The method of claim 1 wherein said subject is [in need of becoming] being treated so as to become infertile or [remaining] to remain infertile.

8. (Amended) The method of claim 7 wherein both β^1 and β^2 confer FSH antagonist activity on said composition; or

wherein both β^1 and β^2 confer CG antagonist activity; or

wherein both β^1 and β^2 confer LH agonist activity[; or

wherein one of β^1 and β^2 confers FSH antagonist activity or lowered FSH agonist activity and the other confers LH agonist activity; or

wherein one of β^1 and β^2 confers FSH antagonist activity or lowered FSH agonist activity and the other confers CG antagonist activity or lowered CG agonist activity; or

wherein one of β^1 and β^2 confers LH agonist activity and the other confers CG antagonist activity or lowered CG agonist activity].

10. (Twice amended) The method of claim 9 wherein

[one of β^1 and β^2 confers FSH agonist activity and the other confers LH antagonist activity or lowered LH agonist activity on said composition; or]

both β^1 and β^2 confer FSH agonist activity; or

both β^1 and β^2 confer LH antagonist activity.

11. (Twice amended) A glycosylated or nonglycosylated composition of the formula

$\beta^2 \approx \alpha\text{-(linker)}_m\text{-}\beta^1$ (1); or

$\beta^1\text{-(linker)}_m\text{-}\alpha \approx \beta^2$ (2)

wherein each of β^1 and β^2 has the amino acid sequence of the β subunit of a vertebrate glycoprotein hormone, or a variant thereof;

"α" has the amino acid sequence of the α subunit of a vertebrate glycoprotein hormone or a variant thereof;

"linker" is a linker moiety; and

"≈" is a noncovalent link between α and β^2;

m is 0 or 1;

wherein each of β^1 and β^2 [confer a different activity on said composition; and

with the proviso that if β^1 is CGβ then β^2 is not FSHβ] <u>is the native β subunit of the same glycoprotein hormone or a variant thereof</u>.

12. (Twice amended) A pharmaceutical composition which regulates the glycoprotein hormone concentrations in a mammal which comprises an effective amount of the composition of the formula

$\beta^2 \approx \alpha\text{-(linker)}_m\text{-}\beta^1$ (1); or

$\beta^1\text{-(linker)}_m\text{-}\alpha \approx \beta^2$ (2)

in admixture with at least one pharmaceutically acceptable excipient; and

wherein each of β^1 and β^2 has the amino acid sequence of the β subunit of a vertebrate glycoprotein hormone, or a variant thereof;

"α" has the amino acid sequence of the α subunit of a vertebrate glycoprotein hormone or a variant thereof;

"linker" is a linker moiety; and

"≈" is a noncovalent link between α and β^2;

each of m and n is independently 0 or 1;

wherein each of β^1 and β^2 [confer a different activity on said composition; and

with the proviso that if β^1 is CGβ then β^2 is not FSHβ] <u>is the native β subunit of the same glycoprotein hormone or a variant thereof</u>.

21. (Amended) The composition of claim 11, wherein β^1 is FSHβ or a variant thereof and β^2 [as] <u>is</u> FSHβ or a variant thereof.

22. (Amended) The composition of claim 11, wherein β^1 is LHβ or a variant thereof and β^2 [as] <u>is</u> LHβ or a variant thereof.

23. (Amended) The composition of claim 11, wherein β^1 is TSHβ or a variant thereof and β^2 [as] <u>is</u> TSHβ or a variant thereof.

24. (Amended) The composition of claim 11, wherein β^1 is CGβ or a variant thereof and β^2 [as] <u>is</u> CGβ or a variant thereof.